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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,787	11/13/2003	Hans Hofland	020681-000410	8755
20350 7590 12/28/2007 TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834			EXAMINER KISHORE, GOLLAMUDI S	
			ART UNIT 1615	PAPER NUMBER
			MAIL DATE 12/28/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/713,787	<b>Applicant(s)</b> HOFLAND ET AL.	
	<b>Examiner</b> Gollamudi S. Kishore, Ph.D	<b>Art Unit</b> 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 30 October 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 31-50 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 31-50 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The amendment dated 10-30-07 is acknowledged.

Since no election requirement is made, the claims included in the prosecution are 31-50.

In view of the amendment to the claims, the 102 rejections over Guo and Szulc are withdrawn.

### ***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 31-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to claims 31 and 43, the lipid phase contains mucoadhesive compounds. A careful review of the specification (0044) indicates that applicant contemplates the use of Carbopol, poloxamers and Carbomers, which are hydrophilic. Therefore, it is unclear as to how the hydrophilic compounds can be present in the lipid phase. One would expect a hydrophilic compound to sequester into the hydrophilic phase and not lipid phase.

Applicant's arguments are not persuasive. Applicant argues that that it is their understanding that the mucoadhesive compounds would recite at the interface of the

water and lipid and they be intercalated with the phospholipid. This argument is not persuasive. A liposome composition contains an aqueous core surrounded by a lipid bilayer and an additional aqueous layer in which the liposomes are in suspension. The compounds such as Carbopol, carbomers and poloxamers soluble in water and also cationic lipids and therefore, one would expect hydrophilic compounds within the aqueous core and in the surrounding aqueous medium and the cationic lipids in the lipid bilayer. Applicant has shown no evidence to the effect that these compounds are part of the lipid bilayer which is against the scientific knowledge. The examples in instant specification do not show when these are added during the liposome preparation. They only show the preparation of liposomes using the phospholipids. The rejection is maintained.

The amended claim recites "said lipid phase comprises 0.01 to 10 wt% phospholipid, 0. 1 to 10 wt % modifying agent and 0. 1 to 10 wt% antioxidant". Taking the maximum amounts of each as 10 %, the total will be 30 %. It is unclear as to what the rest of the lipid phase (70%) contains.

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 31-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo cited (4,804,539).

Guo discloses a method of ocular delivery of ophthalmic drugs for the treatment of eye conditions using cationic liposomes. The liposomes contain phosphatidylcholine, cholesterol (neutral compounds), a cationic lipid and an antioxidant. The liposomes are suspended in an aqueous medium. The amounts of the lipid in Guo are given mole percents. The liposomes further contain mucoadhesive compounds. The active agents taught are anti-viral agents, bacteriostatic agents, anti-allergic agents, anti-inflammatory agents and anti-glaucoma agents (abstract, col. 1, lines 52-65; col. 12, lines 18-29; col. 14, line 43 through col. 17, line 30; Examples particularly V-VIII and claims). The differences between Guo and instant invention are that in instant claims, applicant recites the lipid phase in weight percentages whereas Guo discloses them in mole percentages. Assuming that the weight percentages of the lipids in Guo are different from instant percentages, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts. Similarly, since ocular retention of the applied composition is critical, it would have been obvious to one of ordinary skill in the art to vary the amounts of aqueous medium in which the liposomes are suspended in order to obtain the best retention levels. In the absence of showing Guo however, does not specifically disclose claimed anti-inflammatory agents. Guo also does not specifically teach that the inflammatory conditions are due to different eye

conditions. However, in view of Guo's teachings of generic drugs and the guidance provided, it would have been obvious to one of ordinary skill in the art to encapsulate specific drugs for the various disease states claimed with a reasonable expectation of success.

Applicant's arguments have been fully considered, but are persuasive. Applicant argues that Guo does not teach claimed percentages. This argument is not persuasive since applicant has not shown that the mole percents taught by Guo do not correspond to instant weight percentages. As pointed out above, even assuming that the weight percentages of the lipids in Guo are different from instant percentages, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts. With regard to the active agents, the examiner points out that instant generic claims do not recite any active agent. Furthermore, on col. 14, lines 43-60, Guo teaches several classes of drugs which could be used for the ocular conditions which include anti-inflammatory drugs, anti-cancer drugs, anti-allergic drugs and anti-viral drugs and therefore, it would have been obvious to one of ordinary skill in the art to choose specific drugs from these generic terms and still obtain the desired results.

5. Claims 41-42 and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo cited above, further in view of Touitou (5,716,638).

The teachings of Guo have been discussed above. Although Guo teaches anti-inflammatory agents, does not specifically teach the non-steroidal anti-inflammatory agent (NSAID), diclofenac. The use of diclofenac as the NSAID for the treatment of ophthalmic conditions taught by Guo would have been obvious to one of ordinary skill in

the art with a reasonable expectation of success since the reference of Touitou shows the knowledge in the art of encapsulating diclofenac in vesicular systems (Examples V and XIX).

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Guo. Applicant provides no specific arguments regarding Touitou. The rejection is maintained.

6. Claims 41-42 and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo cited above, further in view of Malerhofer (5,853,753) or vice versa.

The teachings of Guo have been discussed above. As pointed out above, Guo does not disclose specific disorders of the eye which cause the eye inflammation as claimed in claims 34-36 and 49-50 or that the disorders are herpes ophthalmicus or endophthalmitis as claimed in claims 38-39.

Malerhofer discloses liposomal formulations containing active agents for the treatment of eyes diseases of allergic or viral etiology including those caused by herpes virus. The formulations further contain anti-oxidants such as BHT, BHA and vitamins C and E, and gel-forming agents such as Carbopol (abstract; col. 3, line 11 through col. 4, line 25; col. 5, line 50 through col. 7, line 28; col. 10, line 12 through col. 11, line 5; col. 20 line 20 through col. 21, line 30, Experiment 1 on col. 27).

It would have been obvious to one of ordinary skill in the art to use the liposomes of Guo for the various disease states with a reasonable expectation of success since the reference of Malerhofer shows that liposomal formulations containing active agents

are routinely used for these disease states. Alternately, to use the liposomes of Gao in Malerhofer would have been obvious to one of ordinary skill in the art since according to Guo, the amounts of drug which is delivered in drop form in the eye may be substantially higher than that allowable in free solution form, since undesired side effects related to high free drug concentrations are reduced (col. 14, lines 61-65) and since the ocular retention of the drugs is higher (Example VIII).

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Guo. Applicant provides no specific arguments regarding Malerhofer. The rejection is maintained.

7. Claims 31-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schaeffer ((Invest. Ophthalmol. Vis. Sci., 1982) by itself or further in view of Malerhofer (5,853,753).

Shaeffer explores the use of liposomes to enhance intracorneal and Tran corneal penetration of both water ad lipid-soluble drugs using penicillin G and indoxole as the representative drugs. According to Shaeffer, positively charged unilamellar liposomes enhanced transcorneal flux of penicillin G across isolated rabbit cornea more than four fold (abstract; Tables and discussion). It would have been obvious to one of ordinary skill in the art to use cationic liposomes for the delivery of water-soluble and lipid soluble drugs to treat ophthalmic diseases since Shaeffer shows that cationic liposomes are efficient in delivering drugs transcorneally. The differences between Guo and instant invention are that in instant claims, applicant recites the lipid phase in weight percentages whereas Guo discloses them in mole percentages. Assuming that the



weight percentages of the lipids in Guo are different from instant percentages, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts. Similarly, since ocular retention of the applied composition is critical, it would have been obvious to one of ordinary skill in the art to vary the amounts of aqueous medium in which the liposomes are suspended in order to obtain the best retention level. Although Shaeffer does not teach the encapsulation of claimed drugs and the treatment of specific diseases, it would have been obvious to one of ordinary skill in the art to choose appropriate drug to treat specific diseases with reasonable expectation of success since Schaeffer's studies show that both water and lipid soluble drugs can be used with the cationic liposomes.

Malerhofer discloses liposomal formulations containing active agents for the treatment of eyes diseases of allergic or viral etiology including those caused by herpes virus. The formulations further contain anti-oxidants such as BHT, BHA and vitamins C and E, and gel-forming agents such as Carbopol (abstract; col. 3, line 11 through col. 4, line 25; col. 5, line 50 through col. 7, line 28; col. 10, line 12 through col. 11, line 5; col. 20 line 20 through col. 21, line 30, Experiment 1 on col. 27).

One of ordinary skill in the art would be motivated further to use the cationic liposomes of Shaeffer for the diseases claimed since the reference of Malerhofer shows that liposomal formulations containing active agents are routinely used for these disease states. Alternately, to use the liposomes of Shaeffer in Malerhofer would have been obvious to one of ordinary skill in the art since cationic liposomes are more efficient in delivering drugs ocularly as shown by Shaeffer.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant once again argues that Shaeffer does not teach claimed percentages. This argument is not persuasive since applicant has not shown that the mole percents taught by Shaeffer do not correspond to instant weight percentages. As pointed out above, even assuming that the weight percentages of the lipids in Shaeffer are different from instant percentages, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts. With regard to the active agents, the examiner points out that instant generic claims do not recite any active agent and the selection of the active agent depends on the disease to be treated.

8. Claims 41-42 and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schaeffer ((Ophthalmol. Vis. Sci., 1982) by itself or further in view of Malerhofer (5,853,753) as set forth above, further in view of Touitou (5,716,638) cited above.

The teachings of Shaeffer and Malerhofer have been discussed above. These references do not teach the encapsulation of the anti-inflammatory drug diclofenac. The use of diclofenac as the NSAID in the cationic liposomes taught by Schaeffer for the treatment of ophthalmic conditions taught by Malerhofer would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since the reference of Touitou shows the knowledge in the art of encapsulating diclofenac in vesicular systems (Examples V and XIX).

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Shaeffer and

Malerhofer. Applicant provides no specific arguments regarding Touitou. The rejection is maintained.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Gollamudi S Kishore, Ph.D  
Primary Examiner  
Art Unit 1615

GSK